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Post-Traumatic Stress Disorder and Comorbidity

Psychobiological Approaches to Differential Diagnosis

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A striking feature of the psychobiological findings in post-traumatic stress disorder (PTSD), as is reviewed extensively in this volume, is that the nature and direction of neurobiological alterations in PTSD appear to be quite distinct from what has been observed in other psychiatric disorders—even in psychiatric disorders with overlapping symptomatology to PTSD. As such, in addition to providing potential information about pathophysiology, these psychobiological findings have provided some measure of validation for PTSD as a distinct diagnostic entity.

In contrast to the relatively consistent literature supporting PTSD as a biologically identifiable syndrome, prevalence studies have suggested that PTSD as a clinical entity rarely occurs in a discrete or "pure" form. As this chapter will further review later, many studies have now documented that PTSD often co-occurs with other psychiatric disorders. Indeed, if an individual meets diagnostic criteria for PTSD, it is likely that he or she will also meet diagnostic criteria for a major mood or anxiety disorder, alcoholism, substance abuse, or a personality disorder. The uniqueness of PTSD from a biological perspective, then, appears somewhat paradoxical in the face of a clinical phenomenology in which most PTSD symptoms can be found in other psychiatric disorders.

The purpose of this chapter is to consider whether, and to what extent, issues of diagnostic comorbidity or differential diagnosis can be better understood—conceptually and practically—in the context of psychobiological findings of PTSD. Our strategy will be to review the evidence for psychiatric comorbidity and explore the phenomenologic similarities and differences between PTSD and three other disorders—major depressive disorder (MDD), panic disorder (PD) and generalized anxiety disorder (GAD)—that are often associated with PTSD. In this context, we will present and clarify the issues that must be addressed by clinicians performing a diagnostic assessment for PTSD and other possible comorbid diagnoses. Next, we will discuss the potential utility of biological findings to clarify some of these issues, and review laboratory-based abnormalities associated with PTSD for the purpose of identifying those procedures that may be most useful and clinically applicable in distinguishing PTSD from other disorders. Finally, we will discuss

new research findings that may offer new diagnostic approaches.

PSYCHIATRIC COMORBIDITY IN PTSD

PTSD often co-occurs with other psychiatric disorders. The National Vietnam Veterans Readjustment Study (NVVRS), a national epidemiologic survey of PTSD among Vietnam veterans (1,2), (see Chapter 23) found that 50% of veterans with a current diagnosis of PTSD had at least one other psychiatric disorder. According to NVVRS, veterans with PTSD had the following lifetime prevalence rates: MDD, 20%; alcoholism, 75%; drug abuse, 23%; and personality disorder, 20%. Nontreatment-seeking civilians with PTSD have also been found to have high rates of psychiatric comorbidity (3).

Rates of psychiatric comorbidity have been found to be even higher among treatment seekers with PTSD. A 4-week survey of over 100,000 veterans seeking psychiatric treatment at Department of Veterans Affairs (VA) Hospitals across the U.S. in 1986 found that 80% of veterans with PTSD had at least one additional diagnosis, including MDD, anxiety disorders, alcoholism, drug abuse, and personality disorders (4). Reports of lifetime prevalence rates of MDD among treatment-seeking combat veterans with PTSD ranged from 26%–65% (5). Lifetime rates of alcoholism and drug abuse among treatment-seeking PTSD veterans have been estimated at about 60%–80% (6), and lifetime rates of personality disorder ranged from 40%–60% (5).

In considering the reasons for the unusually high incidence of comorbidity between PTSD and other psychiatric disorders, it is important to point out that there is considerable overlap in DSM-III-R (7) diagnoses in general, especially in the anxiety and mood disorders, that likely reflect the considerable overlap of symptoms between anxiety and mood disorders as illustrated in Fig. 1. As can be clearly seen in the Venn diagram, PTSD shares a number of symptoms with MDD, and the anxiety disorders PD and GAD.

With regard to overlap between PTSD and MDD, both syndromes exhibit impaired concentration, diminished interest, and insomnia. Guilt, though no longer an approved symptom of PTSD (it was included in DSM-III [8] but dropped in DSM-III-R), is still considered important, especially by those who believe that pathological grief is also a post-traumatic syndrome (9). In clinical practice, there is often confusion between certain symptoms of PTSD and depression. For example, emotional detachment and restricted range of affect are often confused with depressed mood. Emotional detachment and/or impaired concentration may be confused with psychomotor retardation. Autonomic hyperarousal may be confused with psychomotor agitation. Finally, suicidal ideation is often present in PTSD patients even though it lacks the diagnostic specificity to have been included in the DSM-III-R. A similar analysis could be made of the overlap between PTSD and PD or GAD.

Given this kaleidoscopic shifting of overlapping symptom clusters, it is perhaps not surprising that if an individual meets diagnostic criteria for PTSD, it is likely that he or she will meet DSM-III-R criteria for one or more additional diagnoses. The important clinical issue is, however, whether or not the presence of a comorbid diagnosis constitutes a true concomitant condition (i.e., with a separate underlying cause and pathophysiology), or an apparent one (i.e., due to the artifact of overlapping symptoms). Indeed, it has been argued that when individuals with PTSD also meet diagnostic criteria for MDD, this may actually signal the presence of a single disorder (e.g., a depressive subtype of PTSD) rather than two separate syndromes (5,10). Similarly, association of PTSD with personality disorder (especially borderline or multiple personality disorder) may actually reflect a unitary disorder beyond the detection of current nosological formulations (i.e., as suggested by Herman's (11) conception of "complex PTSD"). The presence of comorbidity, then, may indicate that current definitions of post-traumatic syndromes are too limiting.

Thus, the critical question is whether PTSD is related to other psychiatric disorders in more intrinsic and fundamental ways than simply as a result of nosological artifacts of symptom overlap. Other disorders may indicate comorbidity with the presence of a more expansive response to trauma. Thus, it is certainly possible, that in

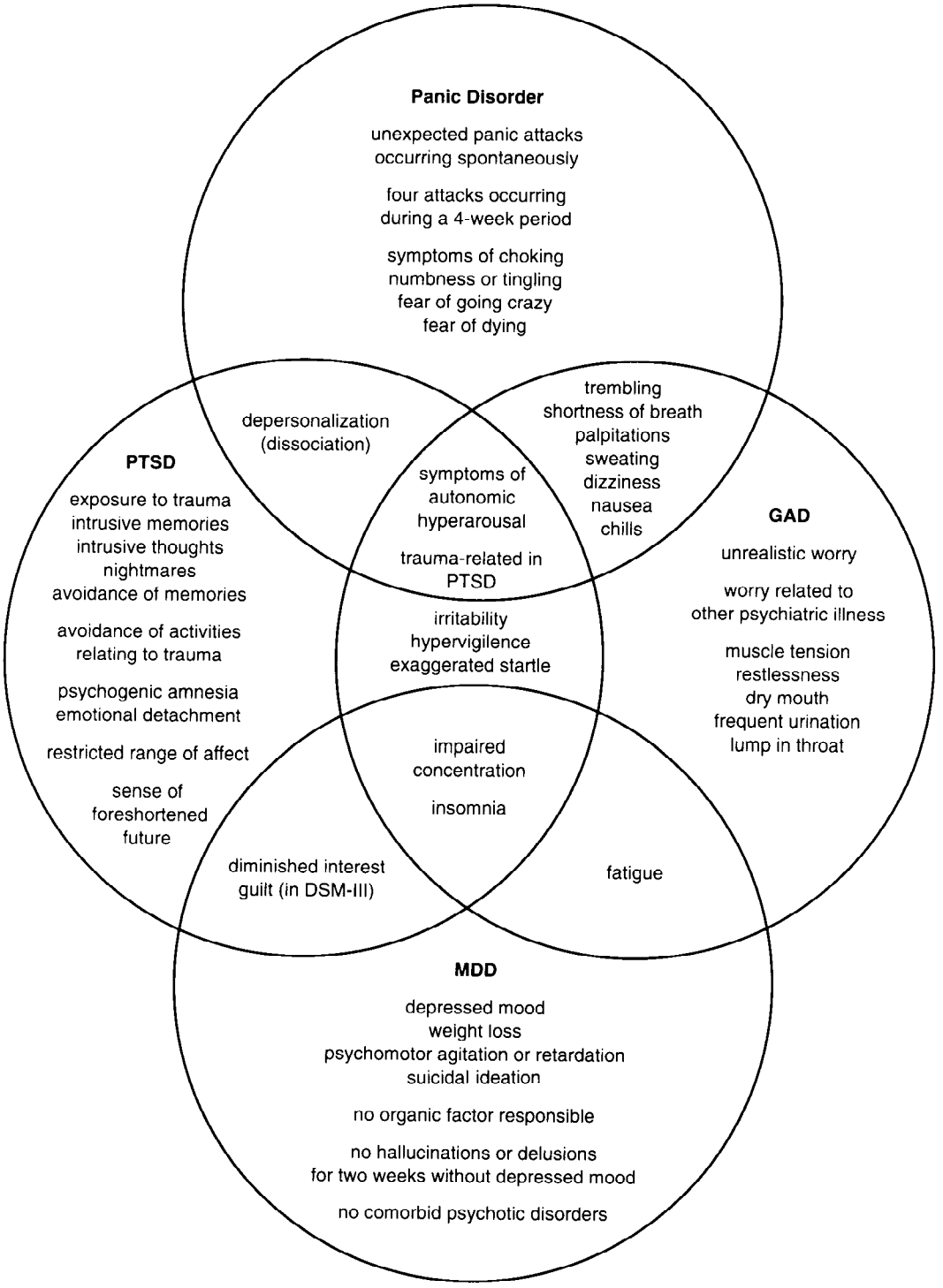

FIG. 1. Overlap of symptoms between post-traumatic stress disorder (PTSD), panic disorder, generalized anxiety disorder (GAD), and major depressive disorder (MDD).

addition to suggesting the presence of subtypes or variants of PTSD, the high comorbidity between PTSD and other psychiatric disorders may reflect different phenomenological expressions of the same underlying pathophysiology (5). Indeed, it has been suggested that stress and trauma are etiologic agents for psychiatric disorders other than PTSD. Furthermore, it can be argued that the concept that stress influences the development and expression of virtually all psychiatric syndromes is an important cornerstone of psychiatry and mental health (Yehuda and McFarlane, in preparation). Thus, in addition to producing a post-traumatic syndrome, a traumatic event may induce or exacerbate a diathesis for other psychiatric disorders. Here the question becomes whether any type of syndrome induced by a trauma, regardless of the specific symptomatology, would be best conceptualized and treated as a post-traumatic adaptation.

In all instances where the occurrence of a comorbid psychiatric illness does not predate a traumatic event, and cannot therefore be definitively identified as a separate (pre-traumatic) entity, it is virtually impossible to determine whether such illnesses constitute distinct comorbid disorders or extensions and variants of the post-traumatic syndrome. However, to the extent that PTSD is associated with a distinct biological profile, which in many instances can be clearly distinguished from alterations occurring in related psychiatric disorders, it is theoretically possible that the interrelationship between these clinical phenomena can be specified more precisely through the use of biological strategies.

Several investigators have provided empirical support for the utility of using psychobiological approaches to complement the DSM-III-R phenomenological assessment of PTSD (12–14). In the next section, we will identify biological and laboratory techniques that may have utility and clinical applicability to the differential diagnosis of PTSD, and critically evaluate their promise and limitations. In doing so, however, it is important to have a conceptual framework that allows for such an evaluation. Table 1 lists five criteria that should be met for a psychobiological assessment procedure to have practical usefulness in the clinical diagnostic work-up of a patient suspected of having PTSD. It will be useful to keep these criteria in mind when evaluating the adequacy of each laboratory test.

TABLE 1. *Criteria for clinical usefulness of a psychobiological assessment procedure*

1. The biological finding obtained through the testing procedure should be highly replicable within and across different laboratories. Furthermore, to have true clinical utility, the testing paradigm should be relatively easy to set up and the information obtained be subject to a relatively unambiguous interpretation by a trained professional.
2. The biological alteration should be reliably present in individuals with PTSD regardless of the type of trauma that has been sustained, and should be differentiable from normals.
3. The biological alteration should not be present in individuals who do not meet criteria for PTSD, even though they may have been exposed to trauma.
4. The biological abnormality should be relatively specific to PTSD and, as such, afford the opportunity of distinguishing PTSD from other diagnostic possibilities.
5. The biological finding, ideally, should be present in individuals with PTSD even if they meet the comorbid criteria for other psychiatric disorders.

PTSD, post-traumatic stress disorder.

LABORATORY ABNORMALITIES IN PTSD

The purpose of this section is not to repeat the review of material presented earlier in this book, but rather to synthesize and evaluate these findings from a clinical perspective. We will also discuss how the identification of psychobiological assessment strategies that have acceptable sensitivity and specificity for PTSD, and that can easily be transferred from the research laboratory to the clinic, ultimately enable us to determine whether comorbid diagnoses assessed by the DSM-III-R are truly distinct disorders or are actually subtypes of PTSD.

Table 2 summarizes the major areas of research on biological abnormalities associated with PTSD. Although it may seem that several types of techniques and methodologies have been used in biological studies of PTSD, it is useful to conceptualize these studies as falling into two major categories: 1) naturalistic, or

TABLE 2. *Laboratory abnormalities in PTSD*

Physiological assessment techniques
Psychophysiological Reactivity
Startle Response
EEG/Sleep Physiology
Event-Related Brain Potentials
Odor-induced EEG
Baseline Neurohormone levels
Catecholamines
Cortisol
Testosterone
Thyroid
ACTH
Endorphins
Urinary Neurohormone Profile
Baseline receptor levels
Lymphocyte Glucocorticoid
Platelet Alpha-2 Adrenergic
Lymphocyte Beta Adrenergic
Challenge Tests[a]
DST
Yohimbine
Stress-Induced Analgesia (With/Without Naloxone)
Clonidine (Growth Hormone)
L-DOPA (Growth Hormone)
CRF (ACTH)
TRH (TSH)

[a]Most physiological assessment approaches are also challenge tests.

PTSD, post-traumatic stress disorder; EEG, electroencephalogram; ACTH, adrenocorticotropic hormone; DST, dexamethasone suppression test; L-DOPA, levodopa; CRF, corticotropin-releasing factor; TRH, thyroid-releasing hormone; TSH, thyroid-stimulating hormone.

baseline observations, and 2) challenge strategies. Naturalistic studies involve measuring components of the particular system of interest under normal, baseline conditions. Ideally, in these studies one examines the biological systems of interest as they function under normative conditions, without external provocation. However, it must be kept in mind that the process of informing an individual that he or she is being evaluated, reviewing potential hazards of the study and obtaining informed consent, attaching electrodes, drawing blood, and other environmental influences may affect the desired measures. Challenge strategies permit evaluation of biological systems under more controlled conditions because they focus on the impact of an external influence (e.g., exposure to a traumatic script or biological substance). When baseline and challenge studies are used in tandem, it is possible to obtain careful information about the nature and origin of biological defects.

Physiological Assessment Techniques

Psychophysiological Reactivity

The earliest attempts to explore the biological basis of PTSD utilized psychophysiological strategies to explore differences in sympathetic nervous system activity under baseline conditions and in response to experimental challenge (e.g., audiotaped sounds of combat, videotaped combat scenes, and, more recently, individualized autobiographical traumatic scripts). In almost all earlier studies, combat veterans with PTSD were found to have higher baseline heart rate, systolic blood pressures, and electromyographical responses compared with normal and combat controls (14). However, later studies did not tend to reveal significant differences between PTSD patients and other groups in baseline measures (15,16). One explanation for the discrepancy between earlier and later studies might be that, as these studies evolved, there was a greater emphasis on methodological details such as psychiatric and medical inclusion/exclusion criteria, and a greater refinement of the psychophysiological protocol in general. (See Chapter 16 for a thorough review of this research.)

In contrast to the lack of consensus concerning the question of baseline psychophysiological differences in PTSD patients compared with other groups, the finding that combat veterans with PTSD show a more dramatic increase in psychophysiological response to combat-related stimuli is unquestionably the most replicable biological finding in the PTSD literature. When exposed to such a stimulus, PTSD subjects exhibit greater cardiovascular arousal as well as increased responsiveness of other autonomic measures such as electrodermal and electromyographic activity. A variety of trauma-related stimuli can reliably evoke this response, including auditory, visual, and olfactory cues. In the case of Vietnam combat veterans, psychophysio-

logical reactivity has been elicited in response to audiotapes of combat sounds (17), videotapes of war zone scenes (18), and a script-driven imagery technique in which the veteran is asked to recollect his own combat experiences (19). This approach has also been used successfully with PTSD patients who have survived motor vehicle accidents (20), Israeli survivors of non-combat trauma (21), and female childhood sexual abuse survivors with PTSD (22). Using the script-driven imagery technique, PTSD subjects could be successfully distinguished from non-PTSD controls with a specificity of 61%–88% and sensitivity of 100% (19,23). In two studies, Vietnam veterans without PTSD were asked to fake their psychophysiological responses to appear more like PTSD veterans. In both cases, it was possible to distinguish the PTSD patients from the non-PTSD comparison subjects (24, 25). Finally, in an innovative extrapolation from this approach, McCaffery et al. (26) detected changes in the electroencephalogram (EEG) in response to trauma-related odors that distinguished PTSD from non-PTSD patients.

Because autonomic hyperarousal is also listed as a symptom of PD and GAD (see Fig. 1), an important question that arises from these studies is the extent to which patients with other anxiety disorders would also show autonomic hyperreactivity. Pitman et al. (27) compared PTSD subjects with a non-PTSD anxiety disorder group (consisting of subjects with PD, GAD, and obsessive-compulsive disorder (OCD). They found that the psychophysiological responses of PTSD subjects were significantly higher than the non-PTSD anxiety group when groups were compared on responsivity to trauma-related scripts. In fact, none of the non-PTSD subjects (including anxious subjects) responded to the script-driven imagery procedure. However, it is important to note that there is no specific reason to assume that patients with PD or GAD would have an intense psychophysiological reaction to a script of a nontraumatic event or traumatic event to which they were not exposed. Perhaps the most stringent test of this paradigm would be to compare traumatized patients with PD or GAD who do not have PTSD with traumatized patients who have PTSD. A comparison of psychophysiological reactivity of the PD, GAD, and PTSD groups to a standard script-driven traumatic imagery process would indicate the specificity of this technique for PTSD assessment.

In this regard, it is also of interest that, although autonomic reactivity to trauma-related stimuli seems to be the most robust psychophysiological assessment technique for PTSD, an exaggerated cardiovascular response can also be elicited in response to a neutral stimulus such as a burst of white noise (28). It is not clear, however, whether this approach has the specificity and sensitivity achieved with trauma-related stimuli.

In assessing the potential utility of psychophysiological reactivity as a laboratory measure to aid in diagnostic assessment, it can be concluded that reactivity as assessed by the cardiovascular response to trauma-related stimuli stands out as one of the best-tested and most feasible psychodiagnostic procedures at this time. It has high specificity and sensitivity, and is difficult to fake. There is sufficient collective experience with this approach so that optimal instrumentation for a psychophysiological laboratory has been determined and an optimal psychophysiological protocol has been established. Furthermore, the script-driven traumatic imagery technique developed by Pitman, Orr, and associates (19) can be used with any trauma survivor. The autobiographical scripts can be carefully crafted to reflect the uniqueness of both the traumatic event and the immediate post-traumatic reaction.

An endorsement of this approach must be tempered, however, by the fact that this method has not been adequately tested on nonveteran cohorts. Therefore, despite its remarkable performance with PTSD patients exposed to war-zone stress, there are only a few preliminary studies in which nonveteran cohorts (such as victims of sexual assault or survivors of motor vehicle accidents) have received psychophysiological assessment. Furthermore, as just described, it is unclear how well this test can distinguish PTSD from other anxiety disorders (e.g., PD, GAD, OCD).

Startle Response

A second indicator of physiological reactivity characteristic of PTSD is the startle response. Indeed, an exaggerated startle response is mentioned as a diagnostic symptom of PTSD. As shown in Fig. 1, however, it is also listed as a symptom of GAD. Startle is usually measured as the latency and amplitude of the eyeblink response to a burst of white noise. Since it has also been shown that this response can be modulated (facilitated or inhibited by nonstartling acoustic prestimulation), another approach is to monitor the degree of facilitation or inhibition rather than the eyeblink reflex itself. Evidence suggests that the startle response in PTSD is an abnormal reflex differing from that seen in normal subjects or patients with panic disorder (29,30). In comparison with non-PTSD subjects, PTSD subjects exhibit shorter latency and increased amplitude of the acoustic-eyeblink reflex (30–32). Ornitz and Pynoos (33) monitored modulation of the startle response in children with PTSD and found that these subjects exhibited a significant loss of the normal inhibitory modulation of startle, suggesting that the traumatic experience had induced a longlasting brainstem dysfunction. Ornitz and Pynoos' study is also unique because it is one (of only two) studies in which a psychobiological approach was tested in children with PTSD. This technique has the distinct advantage over structured interviews and other traditional assessment approaches in that it can be used with preschool children who have neither the linguistic nor conceptual capacity to provide verbal responses or understand abstract ideas.

There have been a number of studies of the startle response in other anxiety disorders. In two studies by Shalev and associates, the acoustic-eyeblink reflex in PTSD has been compared with the startle response in other anxiety disorders such as PD, GAD, and OCD. In the first study, PTSD patients compared to anxiety disorder (PD, GAD, OCD, etc.) patients exhibited a startle response that was significantly greater (30). In the second investigation, it was found that the benzodiazepine, alprazolam, could block the startle response in PD but not in PTSD patients, suggesting a qualitative difference between the startle response in these two disorders (34). Another difference between PTSD startle and that seen in other anxiety disorders is the lack of habituation of this response in PTSD, in contrast to habituation seen in PD, GAD, and OCD (31, 34). Furthermore, alprazolam accelerates startle habituation in PD but not in PTSD (34). A great deal of additional information is needed, however, before concluding that the startle response can be used as an aid in clinical assessment. Since increased startle has been found in other anxiety disorders (29), the extent to which this test can actually differentiate PTSD from other disorders is uncertain. Unless the magnitude of the typical startle response seen in PTSD is so much greater than the startle response seen in GAD, PD, OCD, etc., it may not have much clinical applicability in the differential diagnosis of PTSD.

EEG/Sleep Physiology

Another important use of psychophysiology is in the study of sleep. It is well known that most PTSD patients experience insomnia, and that traumatic nightmares are unique events that differ from classic nightmare/night terror Stage 4 episodes as well as dream anxiety attacks associated with REM sleep (35–37). What is less clear, however, is whether there are characteristic alterations in sleep architecture associated with PTSD (see Chapter 17). It is unclear whether the disagreements found in the published literature to date can be explained by: 1) methodological differences between laboratories; 2) diagnostic imprecision with respect to accurate identification of PTSD patients; 3) interpretive problems because of the frequent association of PTSD with MDD (since MDD does produce its own unique abnormalities in sleep architecture); 4) complicated abnormalities that will not be detected by traditional techniques for monitoring the sleep cycle; or 5) all four of the factors just mentioned. At this point in time, it can be stated that the sleep abnormalities regularly found in

PTSD (increased sleep latency, decreased time asleep, increased awakenings, and increased nocturnal movements) are either too nonspecific or that changes in sleep architecture reported by different investigators are too controversial for the sleep EEG to be useful as a psychobiological assessment strategy.

Event-Related Brain Potentials

The fourth psychobiological abnormality found in PTSD has been reported in two studies. Paige et al. (28) reported a robust difference in the event-related brain potentials (ERPs) recorded in PTSD as compared to non-PTSD patients. In response to increasing intensity of auditory stimulation, the PTSD patients showed a reduced amplitude of the P2 component of the ERP. Using a different procedure with low-intensity auditory stimuli, McFarlane et al. (38) observed delayed N2 and attenuated P3 components of the ERP response among PTSD patients in contrast to normal controls. Despite their intrinsic interest, these findings will have to be replicated before ERP recordings can be considered a potentially useful diagnostic strategy.

Baseline Neurohormone Levels

Catecholamines

Mean 24-hour concentrations of urinary norepinephrine (NE) have been reported elevated in combat veterans with PTSD compared with patients in several other diagnostic categories, such as major depression and bipolar mania (39), and with normal controls (40). Additionally, combat veterans with PTSD also showed a significant increase in the urinary excretion of dopamine (DA) compared to normals. Excretion of NE and DA, but not epinephrine, (EPI) was found to correlate with severity of PTSD symptoms, particularly intrusive symptoms (41). Pitman and Orr (42) failed to observe significant differences in catecholamines between 20 patients with PTSD and 5 combat controls. However, the mean urinary NE excretion observed in the combat controls (58.0 μg/day) was substantially higher than what has previously been observed for normals.

It is important to note, however, that despite the evidence for increased 24-hour urinary catecholamine excretion, evidence of baseline catecholamine activation has not been observed in studies using biological determinations made over short periods of time. For example, as just reviewed, the majority of studies has not found increases in autonomic measures at baseline, nor have baseline changes in plasma catecholamines or catecholamine metabolism been noted (15,16, 43). It is possible that part of the discrepancy between the findings obtained using a 24-hour urine collection versus a single sample plasma determination is related to the fact that the former method allows an estimate of catecholamine activity over a longer time frame, whereas blood sampling (or even resting psychophysiological assessments) relies on immediate autonomic activity over relatively short periods of time. Differences in hospitalization status, severity of PTSD, comorbidity, current or past substance abuse, or other issues may also account for the discrepancy between the findings obtained from urine versus plasma and psychophysiology studies. Future studies are clearly needed to more carefully address these issues. A more thorough review of this topic can be found elsewhere (44–46).

Cortisol

The finding of low urinary cortisol excretion in PTSD compared to other psychiatric groups and normal controls has now been replicated in several studies. In an initial study, lower mean 24-hour cortisol excretion was observed in nine PTSD patients compared to patients in four other diagnostic groups. This finding has been replicated in both inpatient and outpatient combat veterans with PTSD compared to nonpsychiatric, healthy controls, as well as in nontreatment-seeking civilians with chronic PTSD. The only other study examining 24-hour urinary cortisol excretion in PTSD reported an increased urinary cortisol in PTSD (42). This study, however, was methodologically different from the others in

method of urine collection, radioimmunoassay, and other variables (45). In a recent attempt to replicate their initial findings, Pitman et al. did not observe a significant elevation in cortisol in subjects with PTSD. It should also be mentioned that a recent study examining the circadian release of cortisol over the 24-hour diurnal cycle has confirmed that the basal plasma release of cortisol (i.e., determined by averaging estimates of cortisol from samples obtained every 30 minutes for a 24-hour period) was found to be significantly lower in patients with PTSD compared to patients with major depression and normal controls (45).

Although the results just cited are promising in suggesting that PTSD patients can be differentiated from normals, and from patients with mood and psychotic disorders, it is unclear whether cortisol is low in patients with PTSD who also have current comorbid major depression. In one study (47), mean urinary-free cortisol excretion from PTSD patients with MDD was not significantly different from the mean urinary-free cortisol excretion of PTSD patients without MDD. However, additional studies with larger samples are needed before drawing this conclusion definitively.

Testosterone

Serum testosterone concentrations were found to be substantially higher in patients with PTSD compared with patients with major depressive disorder, bipolar mania patients, and normals, but were comparable to schizophrenics. While the clinical characteristics of these findings still need to be explored, the data lend further support to the neuroendocrine distinctness of PTSD and major depressive disorder (48).

Thyroid

Thyroid function tests (TFTs) are well-established clinical laboratory procedures that offer a relatively straightforward technique for distinguishing between PTSD and MDD. Mason and associates (see Chapter 20) have shown that thyroid function is elevated among male Vietnam combat veterans with PTSD. In contrast to non-PTSD control groups, such patients exhibit elevated mean serum total thyroxine (T_4), thyroid-binding globulin, total and free triiodothyronine (T_3), and T_3/T_4 ratios. In fact, Mason has observed that, for some PTSD patients, thyroid indices are at or near the thyrotoxic range. In contrast, when abnormal TFTs are found in depressed patients, such individuals tend to exhibit hypothyroidism (49). Most published reports suggest that when there is a question of comorbidity between PTSD and MDD, elevated TFTs are more likely among PTSD patients and the reverse appears to be the case for MDD. The major limitation of this approach is that most patients with either PTSD or MDD will probably have TFTs within the normal clinical range. Therefore, measurement of TFTs cannot be recommended as a first-line psychobiological assessment strategy for detecting PTSD. Furthermore, it is unclear whether TFTs have any usefulness in the detection of other anxiety disorders.

Plasma ACTH and Beta-Endorphin

Hoffman et al. (50) and Smith et al. (51) have both reported normal adrenocorticotropic hormone (ACTH) levels in PTSD patients compared to normals. The former group, however, reported that beta-endorphin levels were lower at both 9:00 AM and 4:00 PM. Certainly, further studies are needed, since a single stick sample of ACTH or beta-endorphin is virtually uninterpretable in the context of a baseline evaluation.

Urinary Neurohormone Profile

In summarizing whether an assessment of neurohormone levels may have diagnostic utility, as has been previously suggested, (13,44), several points should be considered. As just reviewed, the reproducibility of these findings, particularly with regard to cortisol, has now been documented in several studies. One of the major difficulties with using this approach for diagnostic purposes is that both the lowered cortisol levels and elevated catecholamine levels observed in PTSD are within the normal clinical

(endocrinological) range. Although several psychoendocrine studies have clearly pointed to the fact that hormonal levels need not be outside the medically defined "normal limits" (which reflect glandular disorders) to have clinical significance or practical value in the assessment and management of psychiatric illness, practically speaking, it is currently difficult to determine whether any specific value of one hormone is associated with the presence of a psychiatric condition. It is perhaps for this reason that Mason et al. have suggested that the concurrent assessment of several hormonal systems provides an opportunity to explore differences in hormonal patterns in various psychiatric disorders. Indeed, PTSD appears to be characterized by a specific profile of hormonal changes that is distinct from that of many diagnostic groups and normal controls (although, as with the other biological tests just mentioned, the relationship between PTSD and other anxiety disorders has not been fully evaluated).

Baseline Receptor Levels

Lymphocyte Glucocorticoid Receptors

Steroid receptor-binding parameters are critical to a proper interpretation of studies examining basal hormone secretion, because hormones cannot exert their genomic effects unless they are bound to steroid receptors. Because of similarities in the regulation and binding characteristics of lymphocyte glucocorticoid receptors (GRs) and those in brain, this measure may reflect aspects of central as well as peripheral cortisol regulation. Results from three studies have now demonstrated an increased lymphocyte GR number in combat veterans with PTSD compared with normal individuals, and patients with other psychiatric disorders such as depression, schizophrenia, bipolar mania, and panic disorder (45, 52).

In evaluating the utility of this measure as a potential laboratory assessment, it should be noted that the only major limitation of this test is that, to date, only combat veterans have been studied. If other traumatized groups are found to have similar alterations in GR number, this measure can be of potential usefulness as a laboratory test, as it seems to offer some measure of discrimination between PTSD and other psychiatric disorders, and to a lesser extent between combat veterans with and without PTSD.

Platelet Alpha-2 Adrenergic Receptors

In an initial study, Perry et al. (53) reported a decreased number of platelet alpha-2 adrenergic receptors in 12 combat veterans with PTSD compared to normals. The finding of decreased alpha-2 adrenergic receptors was replicated in a sample of 40 combat veterans with PTSD compared to normals (54). Also observed was that patients with MDD and GAD had significantly higher numbers of platelet alpha-2 adrenergic receptors compared to normal controls and patients with PTSD (54). Platelet alpha-2 adrenergic receptors of PTSD patients showed a greater degree of downregulation or receptor uncoupling (i.e., decreased number of receptors) following in vitro exposure to epinephrine compared with platelets from healthy control subjects. These data support the notion of a chronic catecholamine hypersecretion as reflected by 24-hour urinary catecholamine studies.

Lymphocyte Beta Adrenergic Receptors

Lerer et al. (55) have shown significantly lower basal and forskolin-stimulated adenylate cyclase activity in Israeli combat veterans compared with normals. Adenylate cyclase activity in response to stimulation of nucleotide binding protein and via the receptor linked to PGE1 and phospholipase C activity were normal in the PTSD group. The examination of these second messenger systems has suggested a reduced signal transduction of the beta adrenergic receptor in PTSD. Interestingly, one might hypothesize that a decreased number of beta adrenergic-binding sites due to a loss of beta high-affinity sites (i.e., sites coupled to the nucleotide-binding protein of the receptor-adenylate cyclase complex)

would reduce the activity of the inhibitory nucleotide-binding protein to which this receptor is linked, and would tend to be consistent with an increased (not decreased) catalytic subunit activity in response to forskolin stimulation. Further studies exploring homeostatic regulation of second messenger systems in response to receptor alterations are clearly needed.

In evaluating the utility of measuring adrenergic receptors for diagnostic purposes, it should be noted that no studies have examined any of these receptor parameters in combat veterans without PTSD. Furthermore, although the findings of platelet alpha-2 adrenergic and lymphocyte beta receptor number are relatively consistent among individuals with PTSD, a reduced number of platelet and lymphocyte adrenergic receptors has also been observed in several other medical and psychiatric conditions, (54,55) and appears to reflect a chronic increase in sympathetic nervous system activity, which would by no means be specific to PTSD.

Challenge Tests

Dexamethasone Suppression Test

Studies using the dexamethasone suppression test have continued to show that PTSD patients who are not depressed do not show the classic nonsuppression commonly observed in major depressive disorder. The issue regarding cortisol suppression following dexamethasone in PTSD patients with major depression is less clear. In an initial study, Kudler et al. (56) reported that PTSD patients with major depressive disorder show a comparable rate of nonsuppression to that seen in patients with major depressive disorder, whereas Halbreich et al. (57) and Kosten et al. (58) showed that even depressed combat veterans with PTSD show normal responses to dexamethasone. Olivera and Fero (59) showed a 32% incidence of nonsuppression in 65 combat veterans with PTSD who had a comorbid major depressive disorder. However, these individuals showed normal suppression after their major depression had gone into remission. A study examining the cortisol response to dexamethasone in eight civilian women with PTSD (60) also showed normal responses to this neuroendocrine challenge.

Recently, in order to explore the possibility of enhanced cortisol suppression to dexamethasone (52), Yehuda et al. challenged PTSD patients with 0.50 (10) and 0.25 mg of dexamethasone. A hyperresponsivity to low doses of dexamethasone as reflected by both significantly lower cortisol responses and enhanced translocation of cytosolic lymphocyte glucocorticoid receptors into the nucleus was observed in PTSD patients as compared with normals. Importantly, the hyperresponsivity to dexamethasone was also present in combat veterans with PTSD who met the diagnostic criteria for major depressive disorder. However, in that study patients were not sorted with respect to primary versus secondary MDD, a distinction that may prove important in future studies.

The dexamethasone suppression test (DST) may be a second potential psychobiological assessment approach with sufficient sensitivity, specificity, and feasibility to be considered useful in a clinical context. Here too, however, there must be a conditional endorsement presupposing that hypersensitivity to dexamethasone will be found in PTSD patients who have been exposed to traumatic events other than combat. Furthermore, it will be necessary to show that supersensitivity to dexamethasone among PTSD patients can be reliably demonstrated in several independent laboratories.

Should the hypersuppression to DST be found in other traumatized groups with PTSD, this method would have a major advantage since it is relatively simple to administer. Indeed, the simplicity of this test was one of the major reasons for previous widespread interest in this technique as a potential method for diagnosing MDD. Currently, it does appear that DST can distinguish PTSD from MDD, since the direction of change on the DST is virtually opposite in these two disorders. The MDD patients tend to exhibit nonsuppression in contrast to the hypersuppression seen in PTSD. There is little data to date, however, regarding the DST in

PD, GAD, OCD, or other anxiety or personality disorders. It would be necessary to acquire such information in order to determine the specificity and sensitivity of low-dose DST for PTSD.

What is perhaps most compelling about low-dose DST for PTSD is that the hypersuppression of cortisol observed following dexamethasone administration is compatible with conceptual ideas of PTSD as an atypical stress response (45). Furthermore, the biological abnormality observed on this test represents a descriptor of PTSD that appears to be separate and independent from the psychophysiological assessment procedures described earlier.

Behavioral and Biochemical Response to Yohimbine

Biochemical challenge studies have shown that the selective noradrenergic alpha-2 antagonist, yohimbine, elicits sympathetic arousal as evidenced by increased MHPG levels. Infusion of this drug also elicits panic attacks and Vietnam-related flashbacks in 60% of war veterans tested (61). This response is consistent with the increased peripheral catecholamine excretion and downregulation of platelet alpha-2 adrenergic receptors observed in other studies. It should be mentioned, however, that MHPG increases in response to yohimbine have also been observed in panic disorder.

Stress-Induced Analgesia (With/Without Naloxone)

One of the more provocative neuroendocrine findings in PTSD has been that of a naloxone reversible stress-induced analgesia comparable to that seen in laboratory animals exposed to inescapable stress paradigms (62). In this study, eight PTSD patients reported less pain in response to heat stimulation after viewing a traumatic combat film than eight combat veterans without PTSD. This analgesic response was reversed by the narcotic antagonist, naloxone. Although the data should be considered preliminary due to the small sample size, the findings suggest dysregulation of the endogenous opioid system in PTSD.

Growth Hormone Response to Clonidine and L-DOPA

Jensen et al. (63) found differences in the growth hormone response to clonidine and levodopa (L-DOPA), respectively, in sexually and physically abused boys. In contrast to normals and psychiatric controls who exhibited higher growth hormone levels following challenge with both drugs, sexually abused boys responded only to clonidine, while physically abused boys responded primarily to L-DOPA. The major criticism of the study is that PTSD was not assessed in any of the subjects. Therefore, it is impossible to know whether this approach might be useful in the psychobiological assessment of PTSD.

ACTH Response to CRF

To date, the corticotropin-releasing factor (CRF) challenge test has been utilized to evaluate both hypothalamic CRF secretion and pituitary ACTH activity in psychiatric illness. In several reports, the ACTH response to CRF has been reported to be "blunted" in MDD and anxiety disorders (64–67). A single study of eight PTSD subjects demonstrated that the ACTH response to CRF is blunted as well (51). Therefore, it would appear initially that PTSD patients show the same abnormality as other psychiatric patients in regard to this test.

In interpreting this finding, however, it is important to remember that there are no currently definitive theories as to why ACTH blunting occurs in MDD and anxiety disorders. The fact is, there are several possible explanations for ACTH blunting to CRF and, as previously suggested, given the many different biological routes that can result in ACTH blunting to CRF, and given the already specified differences between PTSD and MDD in other parameters of the HPA axis, it is quite possible that the mechanisms underlying the blunted ACTH response in PTSD are different from those relevant to the blunting observed in MDD (10). Practically speaking,

however, although there may be biochemical reasons for the blunted ACTH response to CRF in PTSD that signify a different pattern of HPA responses in this disorder, as a laboratory test to aid in differential diagnoses this test would not be useful, since the same results are found for PTSD and MDD.

Thyroid-Stimulating Hormone Response to Thyroid-Releasing Hormone

Kosten et al. (58) explored the thyroid-stimulating hormone (TSH) response to thyroid-releasing hormone (TRH) in 11 PTSD patients compared with 28 depressed patients. Rather than the classic blunted thyroid-stimulating response observed in major depressed patients, 4 out of 11 patients showed an augmented response to TRH. This study represents the first attempt to utilize challenge strategies to elucidate hypothalamic-pituitary-thyroid axis dysfunction in PTSD.

FEASIBLE PSYCHOBIOLOGICAL APPROACHES TO DIFFERENTIAL DIAGNOSIS

We believe that only six of the laboratory abnormalities listed in Table 2 can even be considered to have potential clinical applicability at this time. Some tests that are very interesting with regard to theoretical implications and potential practical applications need to be replicated in more than one study before they can be considered for clinical use. These include: 1) measurement of ERPs; 2) odor-induced EEG; 3) baseline ACTH and beta-endorphin levels; 4) stress-induced analgesia; 5) growth hormone response to clonidine and L-DOPA; and 5) challenge tests with CRF and TRH. Some tests would be difficult to set up and standardize in a clinical laboratory. These include measurement of baseline adrenergic and glucocorticoid receptor levels. And some tests are just too complex, ambiguous, and controversial when it comes to interpreting the data (particularly regarding research with the sleep EEG).

In order to be considered useful, a psychobiological assessment procedure should ideally meet the feasibility criteria listed in Table 1. Table 3 shows the six laboratory tests that presently show promise as clinical tools for psychobiological assessment. The table also shows how well each test meets the five criteria in Table 1.

The most promising test at this time is measurement of psychophysiological (especially cardiovascular) reactivity. It has good specificity and sensitivity, is hard to fake, and certainly differentiates PTSD from MDD. It is currently in use in many VA hospitals to complement the clinical and psychometric assessment of patients

TABLE 3. *Feasible psychobiological approaches to differential diagnosis*

Test	Feasibility criteria				
	1	2	3	4	5
Psychophysiological Reactivity	X	X	X	?3	X
DST	X	?1,2	X	?3	X
Startle	X	X	U	?1,3	?4
Thyroid Function Tests	X	U	U	No	U
Yohimbine	X	?1,2	U	?1,2,3	X
Urinary Neurohormone Profile	X	?1,2	U	X	U

X Definitely meets criterion.
? Probably meets criteria but hasn't been adequately tested.
?1: Only tested in one laboratory.
?2: Only tested on Vietnam veterans.
?3: Not adequately tested in other anxiety disorders.
?4: Not adequately tested in PTSD patients with comorbid diagnosis.
U Unknown.
No Does not meet criterion.
DST, dexamethasone suppression test; PTSD, post-traumatic stress disorder.

with war-related PTSD. It is also used informally in VA compensation and disability evaluations, as well as for forensic applications (68). In addition, this technique has been successfully used to assess patients who have developed PTSD following the trauma of sexual assault or motor vehicle accidents. With regard to our feasibility criteria (Table 1), Table 3 shows that specifications for a standardized laboratory procedure and standard assessment procedure have been established (criterion 1), psychophysiological reactivity distinguishes PTSD patients from normal subjects (criterion 2), it's not present in traumatized subjects without PTSD (criterion 3), and it is present in patients who have PTSD plus a comorbid disorder (criterion 5). Some question remains about the specificity of this procedure when it comes to distinguishing PTSD from other anxiety disorders, but preliminary results suggest that it also performs well in that context. In the near future, psychophysiological assessment may become a bona fide part of the routine clinical assessment of PTSD.

The DST, while extremely promising, has only been demonstrated by one group of investigators on one traumatized group (Vietnam veterans), although there have been several replications of DST supersuppression in that laboratory setting. It is a well-standardized clinical laboratory procedure that provides good discrimination between PTSD, MDD, and normals. Future studies must monitor the DST response in PD, GAD, and other anxiety disorders. To date, DST supersuppression has not been observed in non-PTSD subjects. Assuming that Yehuda's work can be replicated in other laboratories and with other than Vietnam veteran PTSD cohorts, DST will meet four of the feasibility criteria in Table 1.

Startle is the only other test listed in Table 3 that may someday stand alone as an assessment technique for PTSD. What is particularly lacking at this time, however, is sufficient research demonstrating that the startle response in PTSD is qualitatively and/or quantitatively different from that seen in other anxiety disorders, especially PD. If Shalev's (34) finding can be replicated, that the PD but not the PTSD startle response can be abolished by alprazolam, this technique may prove very useful as a psychobiological assessment for PTSD.

The measurement of thyroid function tests may complement other approaches but cannot stand alone as a diagnostic strategy. This is primarily because thyroid hormone levels in PTSD are generally within the normal range (although at the high end of the range). It is the pattern of such a hormone profile that has been particularly important in research comparing results in PTSD patients with those of other patients. For example, high normal thyroid indices would be consistent with other tests indicating PTSD but would not be conclusive in their own right. Furthermore, it is unclear whether TFTs have any usefulness in differentiating other anxiety disorders from PTSD. Measurement of thyroid function has become fairly routine from one laboratory to another; the problem with this test is interpretive, not technical.

There seems little potential for clinical application of yohimbine challenge as a diagnostic tool. Although it will distinguish PTSD from MDD, it may not distinguish it from PD. On the other hand, yohimbine challenge may prove to be an excellent technique for monitoring the efficacy of treatment in PTSD patients. As with PD, PTSD patients who exhibited a pretreatment, yohimbine response might be expected to be unresponsive to such a challenge following successful treatment.

MULTIDIMENSIONAL APPROACHES TO DIAGNOSIS

Mason et al. (69) were the first to suggest a multidimensional approach to the evaluation of biological disturbance of PTSD. This suggestion originally stemmed from observations showing that multiple neuroendocrine abnormalities were present in this disorder. The initial multivariate strategies of Mason et al. involved performing baseline assessments of multiple hormonal systems, and using appropriate statistical approaches (e.g., multidimensional scaling) to combine the discriminating powers of each of these hormones to achieve an even greater precision in differentiating PTSD from other psychiatric disorders. Results from this initial study suggested that using cortisol and NE levels together provided a sensitivity and specificity for the diagnoses of

chronic PTSD that were substantially greater than those achieved by other biological markers for psychiatric diagnoses (13,44,69). Furthermore, a multidimensional analysis using a profile of hormones including cortisol, NE, EPI, testosterone, and thyroxine provided classification accuracy approaching 100% in the differential diagnosis of combat PTSD compared to endogenous MDD (13,44). More recently, Yehuda et al. (45) have suggested that, as different neurobiological measures are added to the initial battery of hormones reported in earlier studies (i.e., receptor measures and endocrine responses to challenge strategies), there is a greater potential to enrich and expand the concept of multidimensional analysis in PTSD. For example, utilizing both hormone concentration and receptor number, as well as neuroendocrine responses to challenge, may provide a clearer picture of biological alteration than the assessment of any single parameter individually. What may be helpful, ultimately, is the putting together of a battery that helps address some of the weaknesses and limitations of each tool individually.

From a practical point of view, this elegant approach could potentially be put into practice in most clinical laboratories. Since most hormones measured in PTSD patients are within the normal range, it is essential that biochemical assay procedures be rigorously standardized from one clinical laboratory to the next so that neurohormonal profiles can be calibrated and interpreted consistently wherever they are measured.

SUMMARY

The purpose of this chapter has been to synthesize old rather than to present new information. The goal has been to develop a diagnostic strategy that will improve our ability to diagnose PTSD. We believe that psychobiologic diagnostic strategies will have an important role in future PTSD treatment and research for three reasons: 1) there is a great deal of symptom overlap between PTSD and other psychiatric disorders; 2) PTSD rarely occurs in a "pure" form, but is most often associated with at least one other DSM-III-R diagnosis; and 3) we do not believe that a diagnostic approach such as the DSM-III-R, that relies entirely on clinical phenomenology, can ever achieve the diagnostic precision needed for treatment and research.

Our strategy has been to review the various psychobiological laboratory findings that have been published regarding PTSD, and to evaluate their potential applicability as clinical tools for distinguishing PTSD from other disorders. We have not considered laboratory procedures that have not been replicated, that would be difficult to set up in a clinical laboratory, or that currently appear too ambiguous to interpret.

Our final list is short. We review six potential psychobiologic diagnostic approaches from the perspective of five feasibility criteria. Several strategies appear quite promising, especially psychophysiological reactivity, the dexamethasone suppression test, probably the startle response, and possibly the 24-hour urinary neurohormone profile. We expect that this list will grow and that new clinical applications will emerge as biological research on PTSD is extended to survivors of different traumatic events (besides the Vietnam War), and as PTSD patients are systematically compared with individuals who suffer from other (and comorbid) affective and anxiety disorders.

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